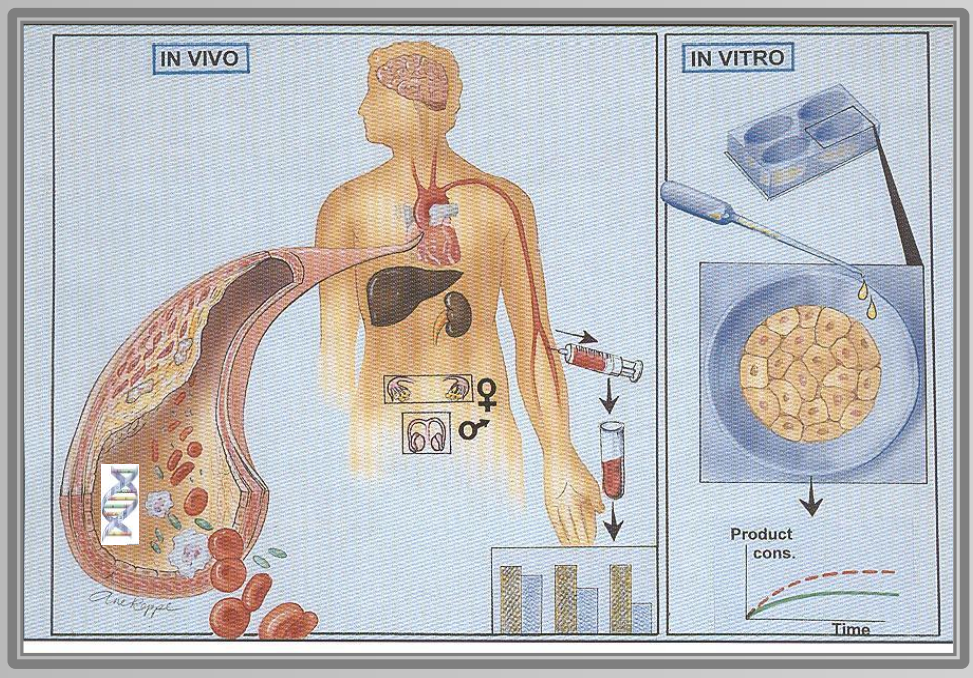


Center for Clinical Heart Research (CCHR)

Department of Cardiology
Division of Medicine
Oslo University Hospital,
Ullevål

"Team building for individual excellence"

Annual Report 2018

http://research.no/clinicalheartresearch/

Content

Preface

Center for Clinical Heart Research (CCHR) is organized within Department of Cardiology, Medical Division, OUS Ullevål. The Center plays an important role as a core laboratory for other research groups in the Department as well as for others in the Division of Medicine and other collaborators.
CCHR is located close to the patients, which is crucial for the scientific activity.

The trademark is researcher-initiated clinical, randomized intervention trials including translational studies on pathophysiological mechanisms in cardiovascular disease states.

The Center has fruitful collaboration with many centers and institutions in which Vestre Viken Trust, Asker & Bærum Hospital, Akershus University Hospital and OUH Rikshospitalet are of special importance by having common PhD-projects and students.
In 2018 further development of laboratory methods related to improved understanding of the innate immune system, the microbial translocation aspects, adipose tissue inflammation as well as to the ageing process, the latter of great importance as our patient populations are getting older.

The high scientific activity has this year resulted in defends of 3 PhD theses and 1 medical student in research's thesis, 19 internationally published papers and further 28 published congress abstracts. Especial to be mentioned is that several of our present PhD-students qualified for oral presentations at different international congresses this year.
Professor emeritus Harald Arnesen has continued as our delegate in the Board for Stein Erik Hagens Foundation for Clinical Heart Research, in addition to take part in the strategy. MD PhD and cardiologist Svein Solheim has continued as medical responsible and also as responsible for several projects.

Through 2018 we have planned for a collaboration with a highly reputated research milieu in Barcelona for one of our post.doc researchers to stay there to perform an interesting project on innate immunity and the possibility for a new clinical treatment modality in patients with myocardial infarction.

We are very pleased to give this annual report for 2018.

March 2019

Ingebjørg Seljeflot (sign)
Professor dr. philos
Center Head

Strategy

The strategies are unchanged

- Systematic researcher-initiated clinical heart research, based on accepted research methodology along with the flow of patients in OUS
- Projects related to acute myocardial infarction, chronic arterial disease, heart failure and atrial fibrillation
- A special focus on ischemic heart disease in diabetics and in the elderly
- Biobanking, standardized sampling and processing of blood and tissue
  About 90 % of all publications are based on biobanks
- Main issue: Studies on mechanisms/translational studies, on biochemical, cellular and genetic aspects especially related to inflammation, remodeling, thrombosis and endothelial dysfunction
- All projects are in line with the strategy for research in Department of Cardiology
- To be an interdisciplinary composed group, including researchers at post.doc level
- CCHR is a group within the network of Center for Heart Failure Research, OUS/UiO and the Regional Research Network for Clinical Microbiota Medicine (CliMic).

Main Goals

The main goals are unchanged

- to increase the understanding of disease mechanisms, pathogenic factors, as well as effects of interventions in patients with cardiovascular disease
- to design and carry out randomized clinical trials, and to further expand on translational research in light of new knowledge and by use of new technology in materials from extended biobanking
- to constitute a dynamic research group with highly motivated participants where group adherence and common efforts lead to progression – for the research group as well as for the individual researcher
  (”Team building for individual excellence”)
- to exert research of high quality, aiming at publications in high rated international journals
- to create an arena for scientific discussions, and for structured research supervision and teaching
- to educate competent PhD candidates a.o. who contribute to academic skill in clinical medicine and research
- to contribute to extended research skill on a post doc level
- to strengthen collaboration with national and international research groups

Organization

Administration and organizational aspects are undertaken by the Center leader. Our most important activity is the regular 2-hour-scientific meetings every 2-3 weeks with PhD fellows, post.docs, laboratory staff, professors and seniors. The main projects are reported with progress, results and relevant discussions. External experts on special relevant topics and co-workers from other groups and institutions, are invited as lecturers.

Application issues for grants are discussed, and research-related scientific and administrative issues are reported.

The PhD fellows are encouraged to give presentations at the meetings and to prepare abstracts for international congresses.

Individual supervision of the single PhD fellows is in addition undertaken, with a ”supervisor-open-door-policy”, and specific projects are separately discussed in smaller groups.

Decisions and Contracts for collaboration with other research groups are based on common scientific interests.

Personnel

Leadership: The leader is also the Head of the R&D Section at Department of Cardiology, 100% position, and professor II at University of Oslo (UiO). In addition, medical responsible is a previous post.doc and cardiologist, and one professor emeritus, the latter the Centers delegate in the Board for Stein Erik Hagens Foundation for Clinical Heart Research, OUS Ullevål.

Employees: 2 medical technologists, of which one with a Master of Science in Biomedicine, 1 post.doc researcher (PhD) and 0.5 study nurse.

10 PhD fellows, 5 post.docs/seniors participate in the milieu and 1 student from the research program for medical students, funded by the Norwegian Research Council via UiO. In addition, the scientific milieu and the laboratory facilities are open for several other PhD-fellows, mainly supervised in collaboration with other groups at the Department of Cardiology, but also from other collaborating groups.

Finances

Budgets for the single projects, including salary for PhD-fellows, technical personnel and running laboratory expenses are based on external fundings from different sources.

The Head is financed from the Department of Cardiology, OUS, Ullevål by a combined position for the Center and for being Head of the Research and Development Section in the Department.

The major economic support from Stein Erik Hagens Foundation for Clinical Heart Research, anchored at Institute of Clinical Medicine, University of Oslo, has been of crucial importance for the activity also in 2018.

Scientific Activities

PhD-theses defended 2018

Cand. Med. Fredrik Wexels: Biomarkers for diagnosis of deep venous thrombosis (DVT) in unselected patients

Supervisors: Ola Dahl MD PhD, Are Hugo Pripp PhD, Ingebjørg Seljeflot Professor

Patients with clinically suspect DVT and Pulmonary embolism (PE) are usually hospitalized. The clinical diagnosis is unspecific and radiological confirmation is necessary. In this study the initial idea was to evaluate the accuracy of a "spot urine stix test" in patients with clinically suspect DVT or PE. Our hypothesis was that the urine stix would have a high negative predictive value and thus a number of patients could be excluded from unnecessary radiological examinations.
We have also investigated stored blood samples from a biobank on markers of activation of coagulation and fibrinolysis, proteomics and other biomarkers for comparison with clinical outcome in the population. The sensitivity of urine measurements was found to be lower than for measures in plasma, and further development of the urine stix is warranted. The study was in collaboration with and initiated at Vestre Viken HF, Drammen. Thesis defended for PhD degree March 2018.

Cand. Med. Vibeke Ritschel: Inflammatory biomarkers in patients with ST-elevation myocardial infarction. Atherosclerotic mechanisms and implication for clinical outcome

Supervisors: Geir Ø. Andersen MD PhD, Ingebjørg Seljeflot Professor, Jan Eritsland MD PhD

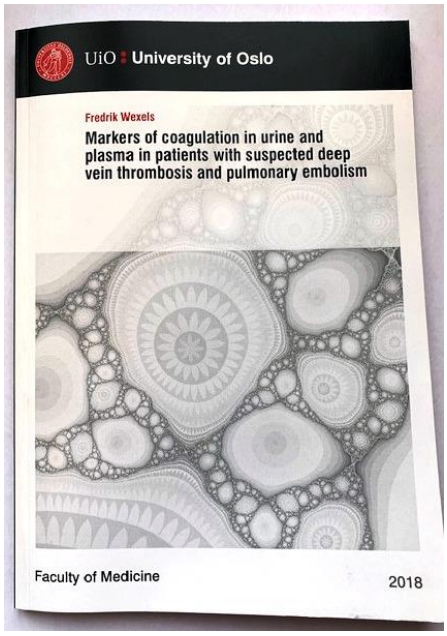
This project is based on "Biobanking of Acute Myocardial Infarction (BAMI)" (vide infra) in which patients admitted to the coronary care unit with an ST-elevation myocardial infarction at OUS, Ullevål, are included. This cohort of patients has been followed for clinical events after 4-5 years (available during 2015). In this specific project inflammatory signalling pathways are explored, especially related to the interleukin-6 axis (IL-6, IL-6 Receptor and Gp130) and CTGF (Connective Tissue Growth Factor). Association studies at inclusion and prospective studies on the predictive role of these markers on clinical endpoints were undertaken. The goal was to extend our understanding of these novel signalling pathways along with the present acute myocardial infarction and the remodelling process, and their role as risk markers for future cardiovascular events. Four papers on the topic have been published and the thesis was defended for PhD November 2018.

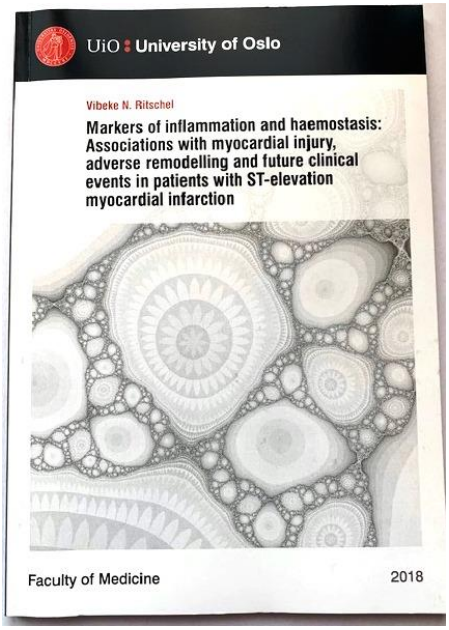
Cand. Med. Anja Wiedswang Horjen: **High-sensitivity Troponin I in atrial fibrillation - Impact of rate and rhythm control and associations to other biomarkers**

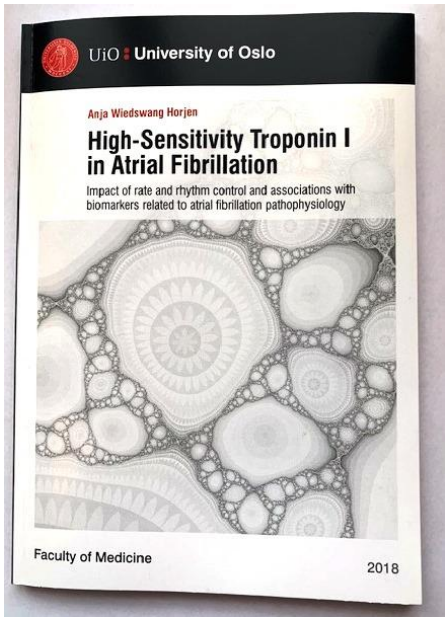
Initiated at Vestre Viken HF, Asker & Bærum Hospital

Supervisors Arnljot Tveit Professor, Sara Ulimoen MD PhD, Ingebjørg Seljeflot Professor

In the ABAF (Atrial fibrillation in Asker and Bærum community), CAPRAF (Candesartan in the Prevention of Relapsing Atrial Fibrillation) trial and the RATAF-study on patients with atrial fibrillation, the importance of cardiac biomarkers (troponin I) was explored, as related to i) AF per se ii) to electrical cardioversion iii) exercise ECG and iv) use of anti-hypertensive medications (angiotensin receptor blockers, calcium channel blockers and beta-blockers). In addition, troponin I in persistent AF as related to NT-proBNP and markers of inflammation and haemostasis was investigated. Thesis defended for PhD October 2018.







CADENCE (Markers of Coronary Artery Disease During Exercise Testing)

Cand. Med. Joanna Cwikiel

Supervisors Arnljot Flaa: MD PhD, Eivind Berge MD PhD, Ingebjørg Seljeflot Professor

The aim of this study is to examine whether changes in N-terminal fragment of pro-BNP (NT-pro-BNP) and troponin T during exercise may improve the accuracy of exercise ECG in the diagnosis of CAD. All subjects (n=300) are examined with coronary angiography, which is regarded as the gold standard for diagnosing CAD. We further aim to clarify mechanisms related to sudden cardiac death as related to exercise by studying whether ischemia may potentiate increase in biomarkers of thrombosis and inflammation.

The results may have important clinical implications for non-invasively diagnosing CAD, especially in women. Furthermore, the study may provide important insights into mechanisms responsible for exercise-related myocardial infarction. The results are presented in two accepted papers, and will be combined with the main results presented in two other papers, for the doctoral thesis, planned to be submitted for evaluation during Spring 2019.

Inflammation and ischemia/reperfusion injury in STEMI patients treated by PCI and ischemic postconditioning

Cand. Med. Christian Shetelig

Supervisors: Geir Ø. Andersen MD PhD Jan Eritsland MD PhD, Ingebjørg Seljeflot Professor

From the POSTEMI study on the effect of post-conditioning in the treatment of acute MI, the purpose of this investigation was to identify novel inflammatory pathways involved in acute MI, reperfusion injury and cardiac remodelling. The main objectives were to specifically explore potential chemokines/growth factors, which, based on previous research may be involved in both reperfusion damage but also potential salvage of the vulnerable re-perfused myocardium. Studies on osteoprotegerin (OPG), a member of the TNF receptor superfamily, Interleukin-8, and CTGF have been explored. In addition, the IL-1β- pathway will thoroughly be investigated in the project. The doctoral thesis is planned to be submitted for evaluation during Spring 2019.

Ongoing projects

Studies on Omega-3 fatty acids

Twin PhD students, Cand. Med. Are Annesønn Kalstad at OUS and Cand. Med.Sjur Hansen Tveit at AUH

Responsible/supervisors: Ingebjørg Seljeflot Professor, Svein Solheim MD PhD, Harald Arnesen Professor em, Pål Smith Professor em, Arnljot Tveit Professor

An ongoing clinical trial (OMEMI), started out in 2013 based on the suspected beneficial effects of omega-3 fatty acid supplementation and the limited knowledge about elderly with CAD. The aim is to investigate the effects of supplementation with 1.8 g/day of n-3 PUFAs on top of modern therapy, on cardiovascular morbidity and mortality during a follow-up period of 2 years in an elderly population (≥70-82 years) after having experienced an acute MI. Special emphasis will be paid on the incidence of atrial fibrillation and heart failure in this elderly population. In addition, the study will generate important new knowledge about the elderly with CAD.

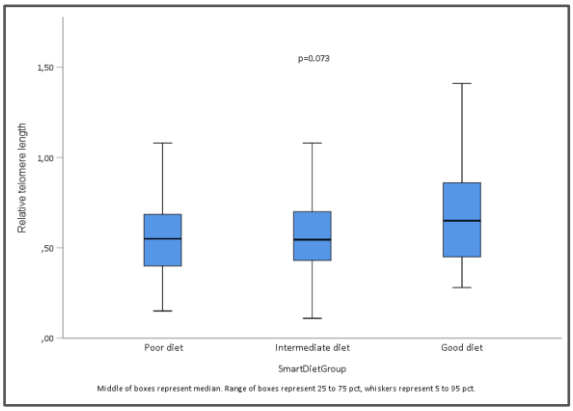
The study is a randomized, placebo-controlled, double blind multicenter study with study center at CCHR. Participating centers are OUS Ullevål, Aalborg University Hospital, Denmark, Akershus University Hospital, Asker and Baerum Hospital and Stavanger University Hospital. The inclusion was finalized by end of June 2018. A large biobank is established for studying mechanisms related to the intervention principle as well as to the process of ageing (vide infra).

Topics addressed:

Omega-3 fatty Acids as related to traditional CVD risk factors and co-morbidities in elderly patients with myocardial infarction (Laake K et al).

Omega-3 Fatty Acids and the importance for myocardial function and cardiac remodeling (Laake K et al).

Diet and Omega-3 Fatty Acids according to "Leukocyte Telomere Length", a suggested marker of longevity as well as proneness for CVD (Kalstad A et al. In press?).



Telomere lenght according to dietary habits. BMC Geriatrics In press

Markers of Ageing / Senescence (telomere length, sirtuins) (vide infra) as related to the presence of atrial fibrillation in the elderly

Studies on Microbial Translocation

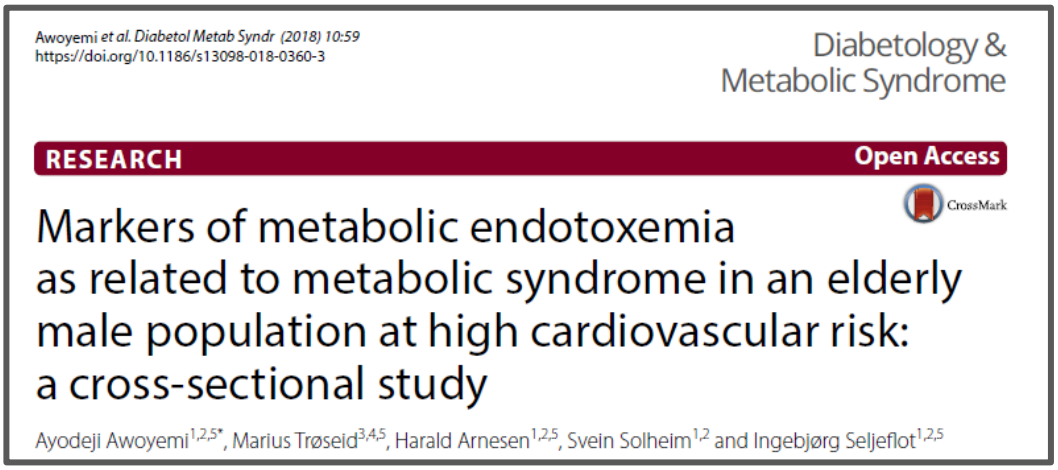
An altered gut microbiota has been linked to several chronic disease states, including obesity, type-2 diabetes and chronic heart failure. Translocation of parts of the gut microbiota, and in particular endotoxins or lipopolysaccharides (LPS) to the systemic circulation, has been proposed to be an early trigger of inflammation, insulin resistance and subsequent cardiovascular risk. LPS promotes inflammation mainly by signaling through Toll like receptor (TLR) 4 on cells of the innate immune system, and CD14 plays a central role by transferring LPS to the TLR4 receptor complex.

Microbial translocation, metabolic syndrome and prognosis

Cand. Med. Ayodeji Awoyemi, PhD student

Supervisors: Ingebjørg Seljeflot Professor, Svein Solheim MD PhD, Marius Trøseid Professor

This project focuse on the potential role of microbial translocation and gut leakage in metabolic syndrome (MetS) and diabetes type-2. The associations between LPS-binding protein (LPB), CD14 and markers of endothelial dysfunction, the degree of atherosclerosis, measured by carotid intima media thickness (cIMT) was published 2018, and the prognostic importance for clinical endpoints are in reviewing process for publication.


Awoyemi *et al. Diabetol Metab Syndr (2018) 10:59*
https://doi.org/10.1186/s13098-018-0360-3

Diabetology & Metabolic Syndrome

RESEARCH Open Access

Markers of metabolic endotoxemia as related to metabolic syndrome in an elderly male population at high cardiovascular risk: a cross-sectional study

Ayodeji Awoyemi[1,2,5*], Marius Trøseid[3,4,5], Harald Arnesen[1,2,5], Svein Solheim[1,2] and Ingebjørg Seljeflot[1,2,5]

Microbial translocation and chronic heart failure

Cand. Med. Ayodeji Awoyemi

In an intervention study on patients with chronic heart failure in collaboration with OUS Rikshospitalet (GutHeart) the effect of treatment with antibiotics and/or probiotics on heart function (ejection fraction) and the leakage markers will be investigated. The inclusion of patient is to be finalized primo 2019 and the main results during 2019.

Scientific Activities- Ongoing Projects

Microbial translocation in HIV patients. Effects of probiota treatment

Main investigator MD PhD Dag H. Reikvam, Dept of Infection diseases OUS Ullevål

Patients with HIV-infection who do not respond on antiviral treatment, so-called immunological non-responders (INR) have an increased low-grade inflammation and systemic immune activation. The hypothesis is that these patients have reduced mucosal barrier, and thus an increased leakage from the gut. We investigate such patients in comparison with responders to antiviral treatment as well as the effect of probiota treatment for 8 weeks. Preliminary results are published at a conference spring 2019.

Microbial translocation in primary sclerosing cholangitis

Main investigator MD PhD Johannes Hov, *OUS Rikshospitalet*

Primary sclerosing cholangitis is a chronic inflammatory liver disease of unknown etiology affecting both intrahepatic and extrahepatic bile ducts, eventually progressing to end-stage liver disease. Recent studies have identified an altered gut microbiota in PSC patients, and the gut leakage hypothesis could be relevant in the pathogenesis. We could show that circulating markers of gut barrier function were elevated in PSC compared with controls and elevated levels associated with reduced liver transplantation-free survival.

Microbial translocation and severe chronic heart failure

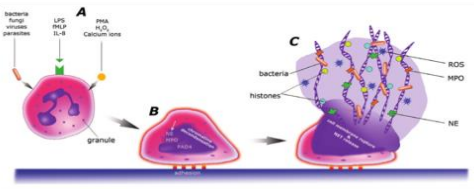
Main investigators: Ass professor Marius Trøseid, MD PhD Johannes Hov

The gut microbiota profile and markers of gut leakage in patients with severe heart failure is investigated to explore whether these are associated with clinical outcome, i.e. heart transplantation and/or mortality. Particular focus is also given to any associations with diet and etiology of the disease. Chronic HF patients had altered gut microbiota composition compared to healthy controls with reduced bacterial diversity, being potentially associated with clinical progression. Main results have been published (2018).

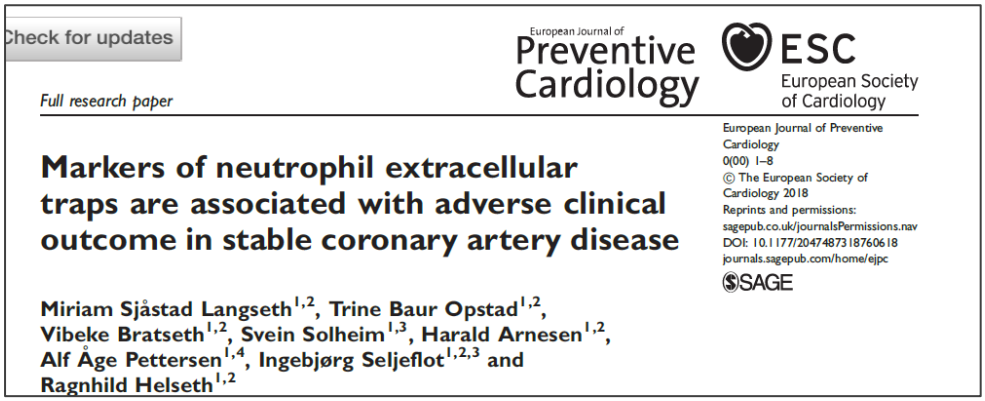
Microbial translocation affected by lifestyle

A project under planning to start during 2019 based on existing biobanks from a long-term exercise study (EXCADI) and acutely induced exercise (CADENCE), as well as from the OMEMI trial in which adipose tissue samples are available, for examination of gut leakage markers as related to dietary habits and intake of very long-chain fatty acids.

Studies on Neutrophil extracellular traps (NETs)



It has become evident that neutrophils upon activation are able to release parts of their nuclear content with residing neutrophil granule proteins into the extracellular space to form spindle-like networks, called neutrophil extracellular traps (NETs), which is thought to induce thrombosis. We have during 2018 published on the relationship between the surrogate markers of NETs, double-stranded deoxyribonucleic acid (dsDNA) and nucleosomes (DNA-histone complexes) and the thrombotic state, as well as its importance for clinical outcome in these patients.


Check for updates

European Journal of Preventive Cardiology

ESC European Society of Cardiology

Full research paper

Markers of neutrophil extracellular traps are associated with adverse clinical outcome in stable coronary artery disease

Miriam Sjåstad Langseth[1,2], Trine Baur Opstad[1,2], Vibeke Bratseth[1,2], Svein Solheim[1,3], Harald Arnesen[1,2], Alf Åge Pettersen[1,4], Ingebjørg Seljeflot[1,2,3] and Ragnhild Helseth[1,2]

European Journal of Preventive Cardiology
0(00) 1–8

DOI: 10.1177/2047487318760618
journals.sagepub.com/home/ejpc
SAGE

NETs in acute and stable coronary heart disease

Cand Med Miriam S. Langseth, PhD Fellow

Supervisors: Ragnhild Helseth MD PhD, Trine B. Opstad MSc PhD, Ingebjørg Seljeflot Professor

The first part of this project is finalized. The second part will explore the importance of NETs markers in STEMI patients undergoing coronary angiography with percutaneous coronary intervention (PCI) and their relation to myocardial injury and left ventricular function (from the BAMI-biobank (vide infra)). The results, showing especial dsDNA to be important for the prognosis in STEMI patients, are under per-review for publication. The third part is also underway, exploring NETosis in patients with post-MI heart failure.

Additionally, in the TASTI-study (vide infra) any presence and location of NETs will be explored in aspirated coronary thrombi from STEMI patients.

NETs in acute myocardial infarction: Impact of glucose regulation

Post doc MD Ragnhild Helseth and MD PhD Eva C Knudsen

An early event during NETs release is decondensation of nuclear chromatin by the enzyme peptidylarginine deiminase (PAD4). In experimental studies NETosis is suggested to be glucose dependent. We could show that acute increase in glucose by an oral glucose tolerance test in STEMI patients lead to upregulated NETosis by PAD4 mRNA levels, indicating glucose to take part in the process.

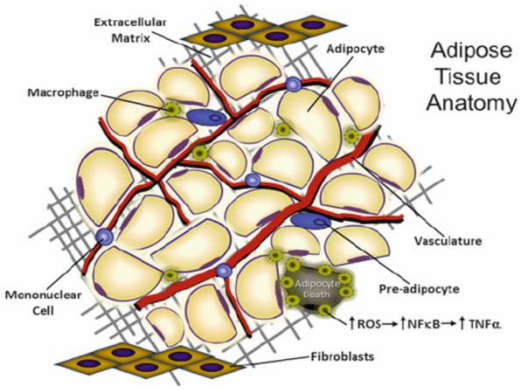
NETs in acute myocardial infarction

Cand med Christian Shetelig and post doc MD Ragnhild Helseth

To further explore any impact of NETs on the the degree of myocardial injury and left ventricular function assessed by coronary magnetic resonance imaging will be explored by use of the biobank from the POSTEMI study (vide supra). Further in vitro studies are planned in collaboration with the ICC Cardiovascular Research Center in Barcelona (2019).

Studies on Adipose Tissue inflammation

We have for several years focused on inflammation and remodeling in the metabolic syndrome, adipose tissue, atherosclerosis and cardiovascular disease states, also with respect to genetic expression of inflammatory and remodeling mediators, visualized in several previous and ongoing projects. Furthermore, differences in fat compartments have been focused.

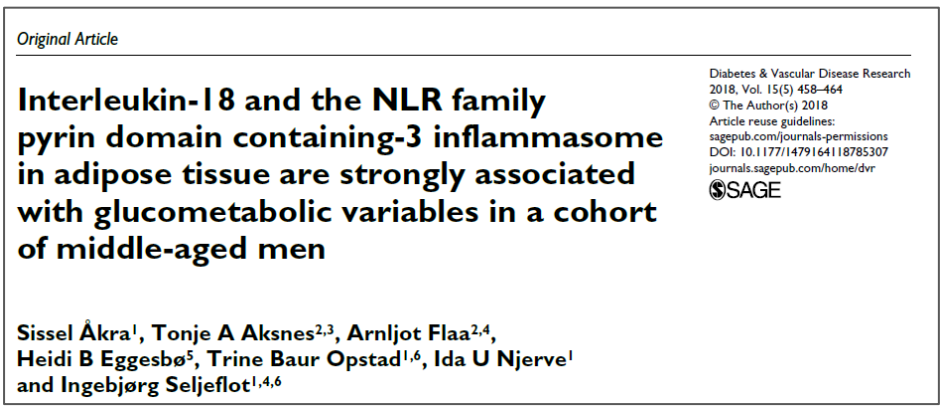


González F et al. Book chapter 2014

Adipose tissue inflammation and remodeling as related to insulin sensitivity in healthy men

MSc Sissel Åkra. In collaboration with MD PhD Tonje A. Aksnes, Section of Cardiovascular and Renal Research, OUS Ullevål

In a cross sectional sub-study of INFO we have shown that there are strong association between insulin sensitivity assessed by glucose clamp, and inflammatory genes of proteins in the inflammasome pathway, expressed in adipose tissue as well as circulating levels, and further that these mediators are related to the amount of abdominal adipose tissue assesses by CT-scan. These results were published 2018. Further, studies on the impact of glucose regulation on markers of adipose tissue remodelling are ongoing. The results will probably shed light on the complex field of early insulin resistance and early obesity.



Original Article

Interleukin-18 and the NLR family pyrin domain containing-3 inflammasome in adipose tissue are strongly associated with glucometabolic variables in a cohort of middle-aged men

Sissel Åkra[1], Tonje A Aksnes[2,3], Arnljot Flaa[2,4], Heidi B Eggesbø[5], Trine Baur Opstad[1,6], Ida U Njerve[1] and Ingebjørg Seljeflot[1,4,6]

Diabetes & Vascular Disease Research
2018, Vol. 15(5) 458–464

DOI: 10.1177/1479164118785307
journals.sagepub.com/home/dvr
SAGE

Adipose tissue inflammation and remodelling in patients with CAD and type 2 diabetes - effects of exercise training. ***Based on the EXCADI biobank***

Cand. Med. Hani Zaidi PhD Fellow

Supervisors: Trine B. Opstad, MSc PhD, Senior Scientist, Ingebjørg Seljeflot Professor, Rune Byrkjeland MD PhD

In this project with patients with CAD and Type-2 diabetes, combined, the adipose tissue regulatory mechanisms of the IL-18/IL-12/NLRP3/Caspase-1 axis were explored based on previous finding of glucose to be important for this regulation. The results are accepted for publication (2019). Further will the MMP-9/TIMP-1/EMMPRIN/axis, reflecting remodeling of the adipose tissue, be investigated, related to glucose control, and to the effects of exercise training.

Inflammatory activity in various compartments of adipose tissue in patients with coronary heart disease (ATICH). ***In collaboration with Department of Thoracic Surgery***

Steering Committee: Professor Ingebjørg Seljeflot, MD PhD Svein Solheim, Professor em Harald Arnesen, Professor Theis Tønnesen, MD PhD Bjørn Braathen.

Executers: In addition to the surgeons

MSc Sissel Åkra: Sample handling

Study nurse Charlotte Holst Hansen: Patient information

Different compartments of adipose tissue like subcutaneous, visceral, perivascular, pericardial and epicardial fat have been claimed to exert different proinflammatory profiles with different associations with cardiovascular disease states.

The aims of this project are to study possible differences in inflammatory gene expression and protein secretion in various compartments of adipose tissue being exposed during open cardiac surgery on patients with coronary heart disease, and valvular disease for control. Inclusion of patients and sample collection have successfully been performed, and laboratory examinations are ongoing.

Studies on Thrombogenicity

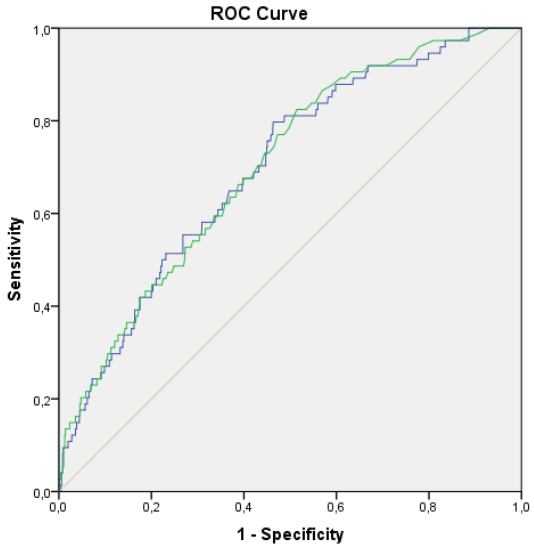
Study on pro-thrombotic activity in STEMI from the BAMI cohort BAMI ("Biobanking in patients with Acute Myocardial Infarction")

A Steering committee for BAMI is established (Professor em. Harald Arnesen, MD PhD Geir Øystein Andersen, Professor Sigrun Halvorsen, MD PhD Jan Eritsland, MD PhD Reidar Bjørnerheim, Professor Ingebjørg Seljeflot, Chair)

In this joint project between the Cardiac Care Unit, General Cardiology Section and CCHR in Department of Cardiology, an extended biobank is mounted along with prospectively registered clinical data and will be the basis for studies on predictive markers for later clinical events. Consecutive patients with STEMI are included after consent. The inclusion of patients ended in 2018, giving a total cohort of about 2000 patients. A PhD project on selected biomarkers were finalized and thesis defended 2018 (vide supra).

Study nurse Charlotte Holst Hansen

has been working on the project, exploring pro-coagulant activity, evaluated by both in vivo and ex vivo thrombin generation analyses for its influence on infarct size and development of heart failure from the first approximately 1000 patients (previously published). The impact of increased pro-coagulant activity on clinical outcome has been further studied, showing especially levels of D-dimer to have prognostic value. The results were published 2018.



Area under the curve	
D-dimer	0.700 (95% CI 0.640-0.758)
NT-proBNP	0.702 (95% CI 0.644-0.760)

Scientific Activities- Ongoing Projects

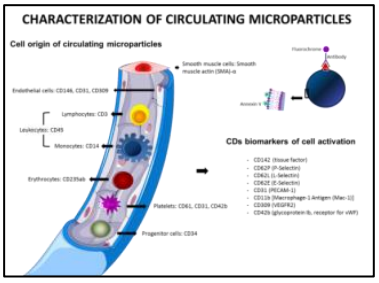
Hypercoagulability, thrombin generation and microvesicles in diabetes - with and without coronary artery disease

MSc Vibeke Bratseth, PhD Fellow

Supervisors: Ingebjørg Seljeflot Professor, Svein Solheim MD PhD, Harald Arnesen Professor em.

The main aims of this project are to assess the importance of glucose control on the hypercoagulable state and on circulating microvesicles (cMVs) in patients with T1DM and in T2DM combined with CAD, and further any association with the degree of atherosclerosis and disease severity. This will be explored in two different cohorts: the EXCADI-biobank of patients with CAD and type-2 diabetes and the Atherosclerosis in Childhood Diabetes study (vide infra) including type-1 diabetics.

The Calibrated Automated Thrombogram (CAT- assay) for *ex vivo* thrombin generation and *in vivo* thrombin generation measurements will be undertaken in addition to flow-cytometry analyses of circulating micro-vesicles (cMVs).



cMVs from different cells are investigated based on their specific cell surface properties

In the EXCADI study special attention has been paid to diabetes patients with albuminuria in whom we previously have shown to be in a hypercoagulable state, and also to the effects of 12-months exercise training on hypercoagulability and cMVs. The results are accepted for publication 2019

The importance of ADAMTS-13 on von Willebrand factor regulation in patients with coronary artery disease – with special reference to aspirin treatment

Ellen Warlo, Medical Student in Research, University of Oslo *(vide infra)*

Supervisors: MD PhD Alf-Åge Pettersen, Professor Ingebjørg Seljeflot

ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin 1 repeats) is a member of the ADAMTS family of metalloproteinases), responsible for the regulation of von Willebrand factor (vWF), which is reported to be a risk factor for coronary artery disease. VWF has pro-thrombotic properties and plays a central role in platelet adhesion and aggregation upon vessel wall injury. ADAMTS-13 is acting by cleaving ultra large vWF multimers into less active fragments. Deficiency of this protease promotes vWF-induced platelet aggregation. In this project we have shown reduced ADAMTS13 is of importance for clinical outcome after 2 years in patients with stable coronary artery disease. Genetic polymorphisms in the gene coding for ADAMTS-13 have been described, and we will further explore such impact on ADAMTS-13 levels as well as on clinical events.

Biomarkers of inflammation and haemostasis: welders under exposure to high-grade pollution

*In collaboration with National Institute of Occupational Health (**professor Dag Ellingsen)***

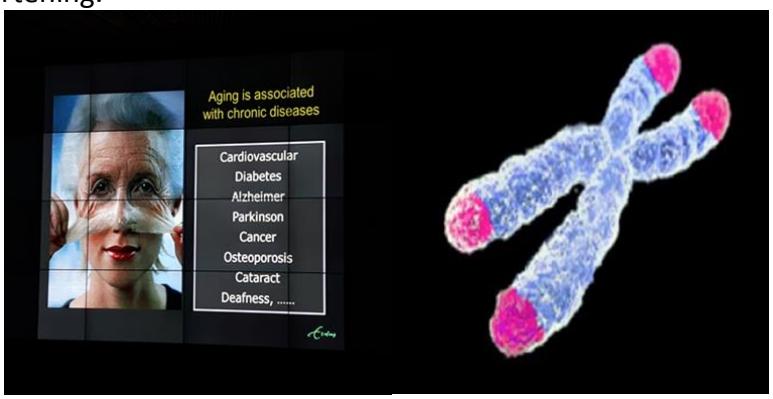
Increased mortality due to pulmonary and cardiovascular diseases by increasing pollution in the external environment has been documented. The mechanisms behind the cardiovascular and pulmonary systems vulnerability to such pollution, are not known. Tunnel construction workers and welders are especially exposed to particulate and gaseous components during work, and our studies have addressed the hypothesis that particles inhaled during work can result in a low-grade chronic pulmonary inflammation inducing a low-grade systemic inflammation.

In Norwegian tunnel workers increased endothelial activation, but reduced inflammation and platelet activation during the work exposition were found (published 2017). We have further investigated a population of russian welders, before and after a 3-year period of daily/weakly work, and could show a pro-thrombotic state with increased thrombin generation and increased endothelial /platelet activation compared to controls.

Studies on Telomere lengths and Ageing

Trine B. Opstad MSc PhD, Are A. Kalstad MD PhD Fellow a.o

A telomere is a region of repetitive nucleotide sequences at the ends of each chromosome which protects DNA at the ends from deterioration. The telomeres become truncated during cell division and about 7 kilobases of telomere length is lost during life. The rate of shortening is thought to be greater in men than in women. Lifestyle and environmental factors have been reported to influence the rate of telomere shortening.



Sirtuins (SIRTs) are a family of NAD+ dependent protein deacetylases, and are highly conserved across species. Sirtuin-1 (SIRT1) is linked to longevity through several pathways of the aging process, including protection from oxidative stress.
We have addressed studies for understanding some mechanisms behind the ageing process in different populations.

Telomere length *as related to myocardial injury and dysfunction in acute myocardial infarction*, as well as to the presence of atrial fibrillation (from the OMEMI trial) (vide supra).

Telomere length *in a population of patients with stable coronary artery disease*, we observed significantly shorter leukocyte telomere length in patient with previous myocardial infarction.

Telomere length *related to other rejuvenating factors in patients with coronary artery disease.*
We observed that higher levels of the growth differentiating factor GDF11 and SIRT1 associated with longer telomeres, accompanied by a reduced pro-inflammatory state. (Results published 2019).

Telomere length *and rejuvenating factors in young and older healthy people*
In an ongoing study we explored the association between leukocyte telomere lengths and other potential longevity factors and pro-inflammatory markers in young and elderly healthy individuals. Any influence of life-style factors and presence of hereditary coronary heart disease are further investigated. Polymorphisms within the telomerase coding genes will be elucidated to further explore the hereditary component.

Scientific Activities - Other

Thrombus Aspiration in acute ST-elevation myocardial Infarction (TASTI)

Jostein Nordeng MD PhD Fellow

Based on results from the "Coronary thrombus genes in acute myocardial infarction", we aim to further explore the cell types and content, in addition to the genetic profile in the aspirated coronary thrombus. Both cellular and non-cellular content of the thrombus will be examined with morphological and immunhistochemical methods and related to time from onset of symptoms to PCI, as well as to the degree of myocardial necrosis. Furthermore, mRNA expression of selected signal molecules will be performed. In addition, peripheral venous blood samples will be analysed for signalling molecules and corresponding mRNA expression in circulating leukocytes. The study is in close collaboration with Department of Radiology and Department of Pathology, OUS Ullevål. Collection of thrombi were finalized early 2018 and laboratory work has started. Main focus will be on pathways related to inflammasome activation, fibrinolysis, remodeling and Netosis (the latter: vide supra).

GLUMIK (Glucometabolic status in patients with acute myocardial infarction)

MD PhD Eva Cecilie Knudsen Post.**doc-projects**

Continuous work by MD PhD Eva Cecilie Knudsen on the aspect of whether antibodies to phosphorylcholine (PC), an important epitope on oxidized low-density lipoprotein (oxLDL) are of importance for clinical outcome after 5.5 years in patients suffering an acute MI. Results are under review for publication.

NORCAST (Norwegian Cardiac Arrest Survival Trial)

A project initiated by **Professor Kjetil Sunde,** Department of Surgical Intensive Care Unit in close collaboration with the Acute Coronary Care Unit by **MD PhD Geir Ø. Andersen** ao. The project has daily been taken care of by PhD-student Henrik Stær-Jensen, also supervised by MD **Espen Rostrup Nakstad**.

Combined clinical-neurological, neurophysiological, neuroradiological and biochemical markers in prognostication after cardiac and/or respiratory arrest. In this multidisciplinary study performed in acute seriously ill patients, 250 patients have been included. Blood samples are taken and processed at CCHR for analysis of a series of biomarkers especially related to neuro-inflammation and thrombotic risk markers in the very acute phase and also after 3 days in those staying alive.

The patients are followed for three years, the last patient during 2018. Due to lack of man power, the biobank has not yet been used.

Diabetes in children and atherosclerosis development

Aida Simeunovic MD PhD Fellow

Supervisors: MD PhD Hanna Dis Margeirsdottir, Professor Knut Dahl-Jørgensen

Patients with type-1 diabetes from childhood have 20-30 times? increased risk for premature death from cardiovascular diseases compared to non-diabetics. In this follow-up study, initiated from Department of Pediatrics/Oslo Diabetes Center, 330 children/youth with type-1 diabetes are compared with 120 healthy controls matched for age and gender to investigate early signs of atherosclerosis as measured with various methods (anatomical, physiological, biochemical). Both groups have been followed for 5 years and the 10 years follow-up is to be finalized early 2018. All blood sampling/processing and facilities for biochemical translational research (biobanking, analyses) are undertaken at CCHR. Two PhD theses have been based on data from this study so far. Part of this study is the basis for the PhD-project of Vibeke Bratseth (vide supra) on hypercoagulability and micro-vesicles in diabetics.

DIALONG (Diabetes type-1: long-term survivors with a new syndrome of late complications)

Cand. Med. Kristine Holte PhD Fellow

Supervisor: Professor Tore Julsrud Berg, Professor em. Kristian Hanssen, MD PhD Svein Solheim

The hypothesis in this study is that patients with long-standing diabetes type-1 have late complication syndrome consisting of cheiropathy and fatigue, in addition to the traditional micro-and macrovascular complications. Markers of glycaemic burden, HbA1c and AGE's, as well as markers of inflammation and endothelial dysfunction are associated with this syndrome. The study consists of 100 patients with a duration of diabetes type-1 for 40 years in comparison to age-matched controls without any signs of related disease for the presence of coronary heart disease assessed by CT coronary angiography, cheiropathy, levels of AGE's in collagen from the shoulder region, inflammatory biomarkers, glycemic control as well as genetic factors.
The inclusion of subjects is finalized and analyses ongoing. Blood sampling/biobanking and analyses of biomarkers for inflammation and endothelial activation are performed at CCHR, and part of the population is also investigated for the ageing aspects (vide supra).

Effectiveness of 24/7 hotline on 30-day readmission following surgical aortic valve replacement surgery: the AVRre randomized controlled trial.

MSc. Stein Ove Danielsen, PhD student

Supervisors: Post doc Irene Lie, Professor Theis Tønnessen, MD PhD Svein Solheim

30-day all-cause readmission after surgical aortic valve replacement (SAVR) yields high readmission rates. Main objective was to determine whether a post-discharge

intervention with a structured telephone follow-up and a 24/7 hotline reduces 30-day all-cause readmissions after SAVR. A prospective randomised controlled trial was conducted and 288 randomly allocated to either usual care or a telephone follow-up system after discharge. Status: All the patients have been included and the main results of the study will be published during 2019.

Laboratory Methods

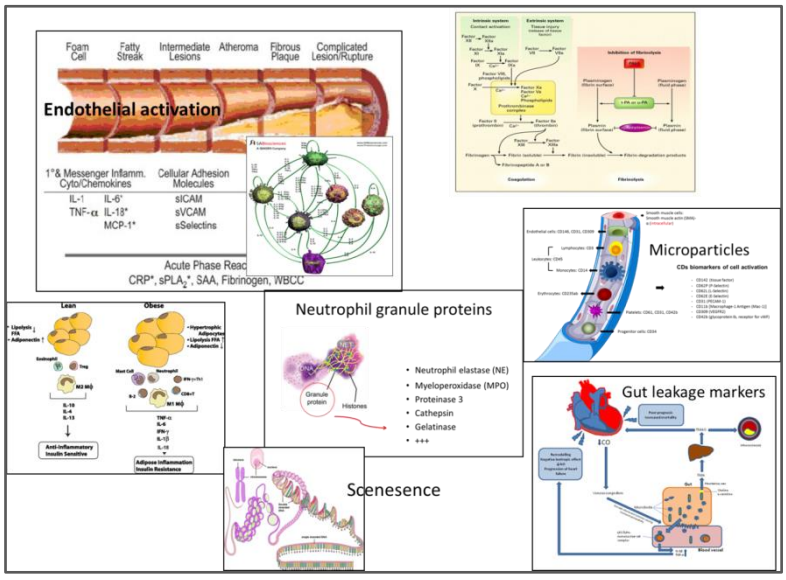
Methods / equipments

- Facilities for blood sampling and processing for biobanking after SOPs (Centrifuges, cooling centrifuges, freezers (-30°C and –80°C))
- Platelet function testing (aggregometry and ”bedside” screening tests (PFA100, VerifyNow)
- Flowcytometry (BD Accuri C6)
- ELISA equipment
- Fluoroscan
- PCR instruments and centrifuges for molecular biology
- ViiA7 RT-PCR (Applied Biosystems)
- Fume cupboard, moveable
- HPLC (Located at Institute for Experimental Medical Research, OUH Ullevål)

- Arrays for gene regulation
- Adipose tissue sample handling/embedding
- PBMC isolation; gene regulation
- Micro RNA, used as a tool for gene regulation of proteins as well as use as biomarkers

Biomarkers of

- Haemostasis
- Inflammation
- Endothelial activation
- Microparticles
- Ageing / senescence (telomere length; sirtuins etc)
- Gut-leakage
- Netosis /NETs markers (innate immunity)
- Remodeling



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